

Niclosamide restricts entry protein CD147 – A novel therapeutic prospect in SARS-CoV-2 infections

- The deadly coronavirus, which caused the COVID-19 pandemic, still remains a concern as it undergoes mutations.
- Researchers across the globe are looking for new ways to block the entry of the SARS-CoV-2 virus into the human system.
- Zhe Yang, postdoctoral research associate, has collaborated with fellow researchers at Professor Xu Liang's lab at the University of Kansas in the USA. They investigated an alternate target to treat people with SARS-CoV-2 infection – the CD147 spike protein.
- They have discovered an RNA-binding protein known as human antigen R (HuR), responsible for the expression of the CD147 protein
- Their work offers hope for a novel therapeutic agent in the long fight against COVID-19.

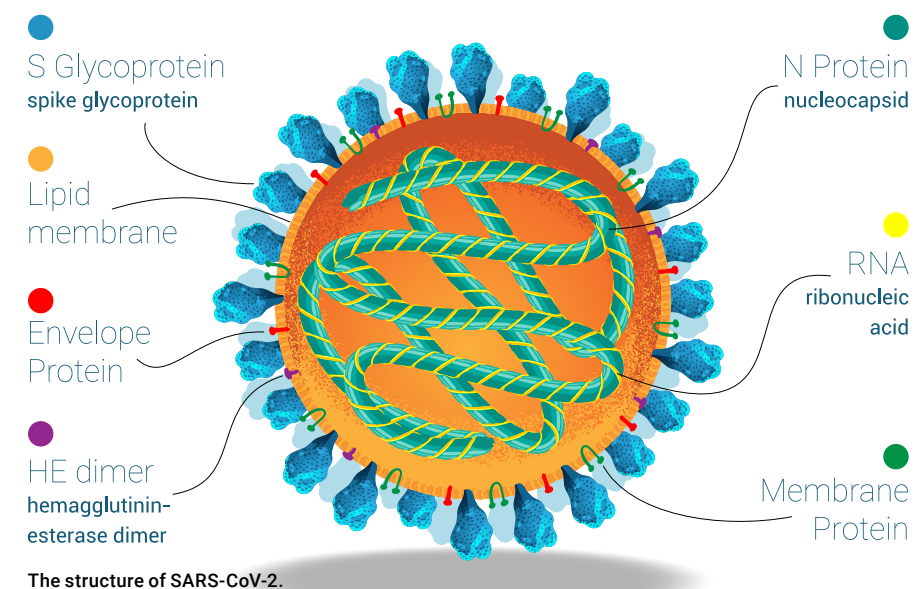
Coronavirus disease (COVID-19) is a highly contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Resulting in almost seven million deaths

worldwide, it is imperative to prevent spread of SARS-CoV-2 and treat it appropriately. Although repurposed medicines (like Paxlovid, Remdesivir, and Molnupiravir) and vaccines have been approved, helping to

establish a much-needed line of defence against SARS-CoV-2, the constant mutations undergone by the virus mean that it remains a threat. The approved medications also have limitations as they are not feasible for long-term use. Moreover, the current vaccines target the S (spike) protein in the SARS-CoV-2, which is prone to undergo multiple mutations, leading to a possible reduction in the efficiency of these vaccines and an increase in the number of variants of concern (VOC) of the virus.

Even people who have recovered from COVID-19 are prone to suffer significantly from its long-term complications, such as multisystem inflammatory syndrome, autoimmune conditions, pulmonary fibrosis, and myocarditis. COVID-19 has been responsible for 767 million reported infections and approximately 6.9 million recorded deaths as of June 2023.

To prevent a further increase in the global health burden, blocking the entry of SARS-CoV-2 into the human system via alternate targets remains a vital therapeutic need. To bridge this gap, Zhe Yang, postdoctoral research associate, has collaborated with



The structure of SARS-CoV-2.

fellow researchers at Professor Xu Liang's lab at the University of Kansas in the USA, to investigate a new target pathway for the treatment of COVID-19.

Repurposing niclosamide

Niclosamide is primarily an anti-parasitic medication and studies show that is effective

Niclosamide is primarily an anti-parasitic medication and studies show that it is effective at inhibiting SARS-CoV and MERS-CoV.

at inhibiting SARS-CoV and MERS-CoV (both members of the coronavirus families). Niclosamide prevents the formation of spike-induced syncytia (a structure with multiple nuclei formed when a virus infects the cell) through the TMEM16 ion channel (a crucial calcium channel in the human body). This implies that it can target viral spike-induced cell infection.

Niclosamide is also a potent mitochondria uncoupler, meaning that it can disable the mitochondria, resulting in a loss of energy supply to a cell and its eventual death. Further, it has also been shown to be effective in inhibiting the final processing of multiple proteins crucial to cancer signalling pathways. Niclosamide also inhibits the maturation and activation of inflammatory cytokines (responsible for chronic inflammation-induced conditions like pulmonary fibrosis, multisystem inflammatory syndrome, etc.) which can be useful in treating patients with long-term complications of COVID-19.

The curious case of CD147

Niclosamide has already been shown to be effective in inhibiting the SARS-CoV-2 along with its multiple variants like the alpha,

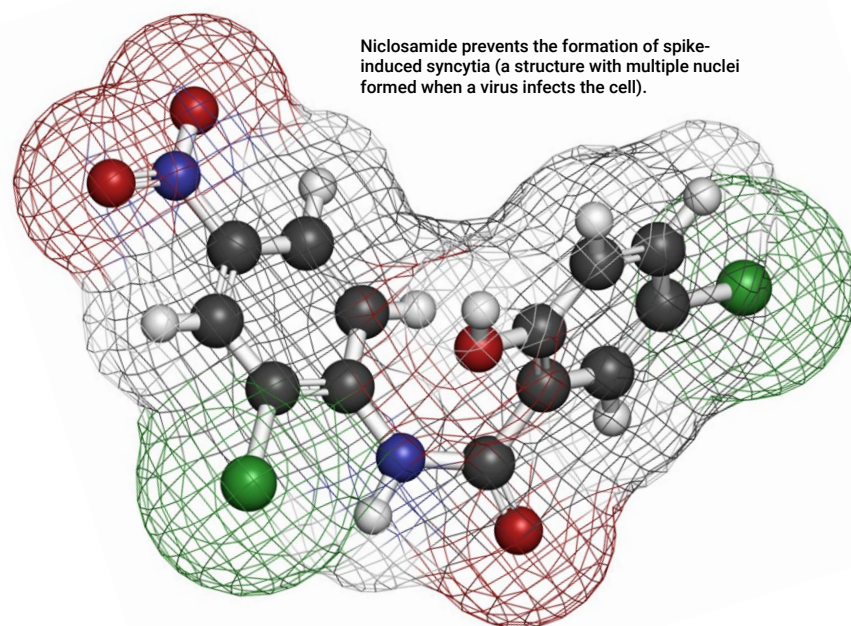
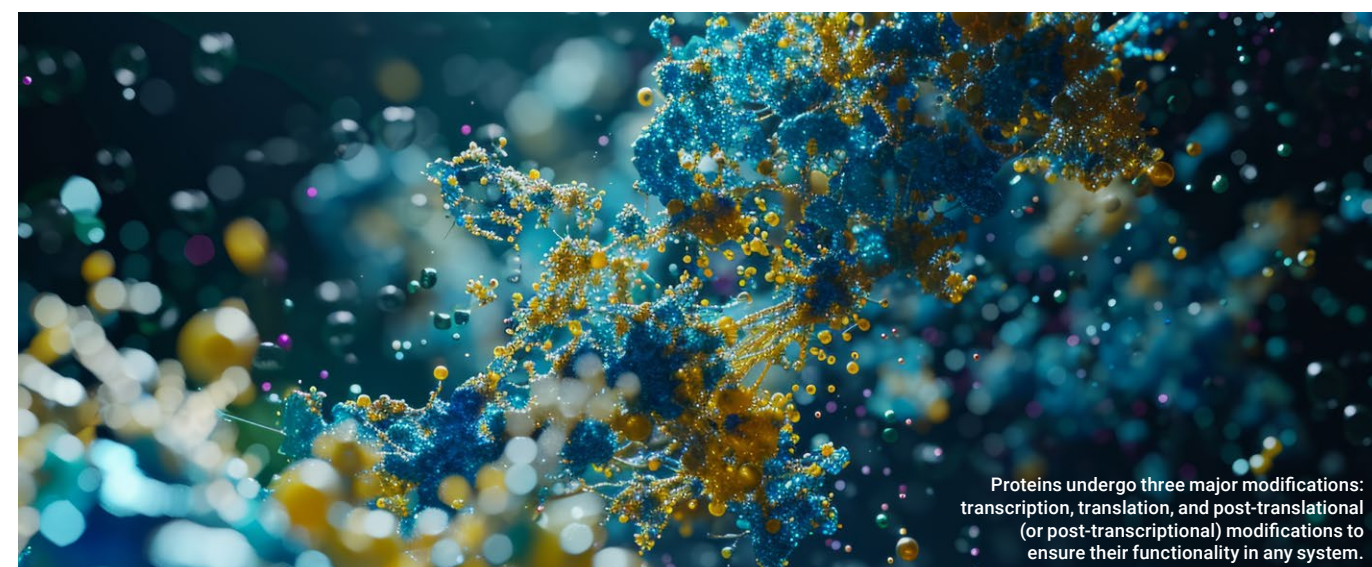
beta, delta, and the more recent omicron. In their research, Yang and colleagues have investigated the possible influence of using niclosamide in preventing the SARS-CoV-2 infection through an alternate pathway by targeting the CD147 protein.

Proteins undergo three major modifications to be synthesised and used by any system they might belong to: transcription, translation, and post-translational (or post-transcriptional) modifications to ensure their functionality in any system. Any interruption in these processes can lead to incomplete development of the protein, thus rendering them useless. Niclosamide is one such inhibitor which prevents the translocation of proteins in the cellular space and interrupts their post-translational modifications.

CD147 (in human cells) is also referred to as Basigin (BSG) or extracellular matrix metalloproteinase inducer (an extremely potent marker of inflammation). It has been shown as an alternate entry point for SARS-CoV-2, in addition to angiotensin-converting enzyme 2 (ACE2). CD147 is also known to influence multiple cancer and viral infection pathways. Even bone marrow and kidney cells have shown an increased propensity to SARS-CoV-2 infection through CD147. This makes CD147 a potent therapeutic target in preventing the entry of SARS-CoV-2 virus.

The discovery of human antigen R (HuR)

Yang and colleagues demonstrated that human antigen R (HuR) – an RNA-binding protein (which binds to the genetic material in cells) was responsible for the development and post-translational modification of CD147, making human cells more prone to SARS-CoV-2 infection. Previous studies also show high levels of HuR in fibrosis models of the lungs, liver, and kidneys, indicating its role in inflammatory diseases as well as multiple cardiac and hypertensive disorders.



Niclosamide successfully inhibited the transcription and post-transcriptional modifications of the HuR protein, blocking its ability to aid the maturation and expression of CD147 on human cells.

Niclosamide successfully inhibited the transcription and post-transcriptional modifications of the HuR protein, blocking its ability to aid the maturation and expression of CD147 on human cells. This protected the human cells from being infected by the SARS-CoV-2 virus.

The future of COVID-19 treatments?

Niclosamide has proven effective in multiple cell lines (including respiratory and cancer cells), by reducing the overall protein levels of CD147 irrespective of location. Not only is this crucial in reducing the global burden of COVID-19, but also beneficial in exploring probable therapeutic actions on tumours and cancers.

Another crucial parameter in this study was assessing if niclosamide could block the entry of a highly-glycosylated spike protein (glycosylation refers to another crucial post-transcriptional modification for certain proteins) through a highly-glycosylated CD147 which is known to cause prolonged complications of COVID-19. The research has shown niclosamide to be successful in this case as well.

This study not only highlighted niclosamide's role in inhibiting SARS-CoV-2 infection and long-term complications, but also sheds valuable light on the potential of HuR as a regulator for multiple pathways leading to inflammation in the body.

Personal response

Are there any other crucial molecular pathways, apart from HuR-CD147, that can be targeted by niclosamide in COVID-19 samples?

This is a great question. Niclosamide regulates several targets that influence its effectiveness:

1. It is believed to hinder viral entry and exit through endosomal neutralisation, effectively preventing the release and maturation of the SARS-CoV-2 genome.
2. Niclosamide also enhances autophagy in primary human lung cells and intestinal organoids by inhibiting S-phase kinase-associated protein 2, thereby reducing the replication of SARS-CoV-2. Additionally, it has been

observed that niclosamide can inhibit viral replication in COVID-19 affected lungs by blocking the formation of spike-driven syncytia in pneumocytes infected with SARS-CoV-2.

Are there any studies exploring the beneficial effects of niclosamide on different forms of cancers?

Yes, niclosamide has shown effectiveness against a range of cancers, including colorectal, lung, breast, head and neck, ovarian cancer, glioblastoma, hepatocellular carcinoma, prostate cancer, and leukaemia. These studies highlight the potential of niclosamide as a promising agent in the battle against cancer.



Details



Professor Xu Liang



Zhe Yang

e: xul@ku.edu
w: molecularbiosciences.ku.edu/people/liang-xu

Funding

The study was funded by NIH and DOD grants.

Collaborators

Drs Yuxia Zhang and Jianming Qiu from The University Of Kansas Medical Center (KUMC).

Bio

Professor Xu Liang's lab has been working on drug discovery for small-molecule cancer therapeutics targeting signalling pathways, especially for cancer cell chemo/radio sensitisation by molecular modulation of apoptosis/autophagy/necroptosis. Currently, Liang is working on cancer drug discovery, using structure-based rational drug design for novel small-molecule inhibitors targeting Musashi-1/2 and HuR, the 'undruggable' RNA-binding-proteins.

References

- Yang, Z, Zhang, Q, Wu, X, et al, (2023) Repurposing niclosamide as a novel anti-SARS-CoV-2 drug by restricting entry protein CD147. *Biomedicines*, 11(7), 2019.
- Rabaan, AA, Al-Ahmed, SH, Albayat, H, et al, (2023) Variants of SARS-CoV-2: Influences on the vaccines' effectiveness and possible strategies to overcome their consequences. *Medicina (Kaunas)*, 59(3), 507.
- Lin, L, Li, Q, Wang, Y, et al, (2021) Syncytia formation during SARS-CoV-2 lung infection: a disastrous unity to eliminate lymphocytes. *Cell Death Differ*, 28(6), 2019–2021.
- Mengist, HM, Kombe Kombe, AJ, Mekonnen, D, et al, (2021) Mutations of SARS-CoV-2 spike protein: Implications on immune evasion and vaccine-induced immunity. *Semin Immunol*, 55, 101533.